analgesia). This is due to a previously impossible passage of the drug through the bbb which could be achieved by one or more of the following mechanisms: enhancement of the transport of the drug through the bbb by diffusion or by an activation of endocytotic uptake by endothelial cells of the brain blood vessels.

Theoretically, there are some possibilities to influence the penetration of drugs through the bbb either by the use of active transport or by passive ways.

Polysorbate 80 is a very interesting substance in this respect for brain targeting and enhancement of the uptake of some substances. Tröster, S. D., Muller, U., Kreuter, J., "Modification of the body distribution of poly (methyl methacrylate) nanoparticles in rats by coating with surfactants." *Int. J. Pharm.* 61:85–100(1990), demonstrated an increased accumulation of nanoparticle radioactivity in the brain area after i.v. injection of polysorbate 80-coated 14C-poly(methyl methacrylate) nanoparticles. However, the same paper also showed similar uptake with other surfactants in the brain. Since these polymers are only very slowly biodegradable, this accumulation within the time frame of the mentioned study has to be due to intact particles.

However, as mentioned before and as shown in FIG. **2** and Table 1, the simple mixture of nanoparticles with surfactants as used in the Tröster study did not lead to any transport of the drug across the bbb. In an earlier study by Kreuter, J., Hartmann, H. R., "Comparative study on the cytostatic effects and the tissue distribution of 5-fluorouracil in a free form and bound to polybutylcyanoacrylate nanoparticles in sarcoma 180-bearing mice." *Oncology* 40:363–366(1983), an enhanced 5-fluorouracil accumulation into the brain was observed in comparison to a free solution of the drug after using nanoparticles prepared in a Polysorbate 20-containing medium. At that time, this result did not attract any attention, since the binding to nanoparticles induced an increased 5-fluorouracil concentration in all organs investigated. In addition, the same situation as in the Tröster study likely occurred in that the particles accumulated in the blood stream of the brain without crossing the bbb. As mentioned above, the induction of dalargin activity in the present invention was possible only after binding to nanoparticles and only after attainment of an equilibrium binding of the drug. Mixing of this drug, Polysorbate 80 and the nanoparticles and the i.v. injection immediately after mixing exhibited no drug action at all. This clearly demonstrates that the activity was only due to drug bound to intact particles.

The mechanism of the transport induction could be due to a number of mechanisms. First, nanoparticles may be bound to the inner endothelial lining of the brain capillaries. Subsequently, the nanoparticles would just deliver the drug more efficiently to the brain cells by providing a large concentration gradient and simple diffusion. The second possibility is brain endothelial uptake by phagocytes. As we have shown in the in vitro study above, Polysorbate 80 induces an increased tissue uptake of nanoparticles in brain blood vessel endothelium. Again, the drug could then be delivered by diffusion out of the endothelial cells to the brain cells. Alternatively, but probably less likely, the nanoparticles with the drugs could be exocytosed into the surrounding brain tissue.

The possibility exists that Polysorbate 80, moreover, seems to have bbb-opening properties. Sakane el al. (1989) showed that a 9% solution of Polysorbate 80 provided an enhanced passage of insulin and the dipeptide b-kyotorphin through the bbb in the brain. However, with the in vivo experiment above, we have clearly shown that this can be ruled out as a possible mechanism. Because group 4 (mixture of dalargin solution and Polysorbate 80) did not show analgesia on the tail flick test, the Polysorbate alone does not result in dalargin passage. Thus, our method provides a specific bbb passage method which clearly displays an unexpected improvement over the prior art. The mechanism is not one of nondiscriminant opening of the bbb itself to a CNS-active drug.

What is claimed is:

1. A method of transmitting a pharmacologically active substance across the blood-brain barrier in a mammal to achieve a pharmacological effect in the central nervous system comprising the steps of:

loading a nanoparticle with said pharmacologically active substance by absorption, adsorption, or incorporation thereto;

coating said loaded nanoparticle with a surfactant selected from a group consisting of polyoxyethylene 20 sorbitan monolaurate, polyoxyethylene 20 sorbitan monopalmitate, polyoxyethylene 20 sorbitan monostearate, polyoxyethylene 20 sorbitan monooleate, and mixtures thereof;

administering said coated nanoparticle to said mammal in a manner which allows said drug to enter the bloodstream whereby said pharmacologically active substance reaches and crosses the blood-brain barrier; and

allowing said pharmacologically active substance to achieve said pharmacological effect.

2. The method of claim **1** wherein said loading step comprises mixing said pharmacologically active substance and said nanoparticle in solution and allowing sufficient time for an amount of said pharmacologically active substance which provides the pharmacological activity of said active substance to be adsorbed by said nanoparticle.

3. The method of claim **1** wherein said loading step comprises incorporation of the pharmacologically active substance into the nanoparticles by manufacturing the nanoparticles in the presence of said pharmacologically active substance.

4. The method of claim **1** wherein said coating step comprises mixing said loaded nanoparticles with a solution of said surfactant in a solution and allowing sufficient time to allow said surfactant to coat said nanoparticle.

5. The method of claim **1** wherein said administration step comprises oral administration.

6. The method of claim **1** wherein said administration effect comprises intravenous administration.

7. The method of claim **1** wherein said nanoparticle comprises a synthetic polymeric particle from about 1 to 1000 nm in diameter.

8. The method of claim **7** wherein said synthetic polymeric nanoparticle are formed of a polymer selected from the group consisting of acrylates, methacrylates, methylmethacrylates, cyanoacrylates, acrylamides, polylactates, polyglycolates, polyanhydrates, polyorthoesters, gelatin, albumin, polystyrenes, polyvinyls, polyacroleines, polyglutaraldehydes, and copolymers, and mixtures thereof.

9. The method of claim **7** wherein said nanoparticles are formed by a method selected from the group consisting of emulsion polymerization, interfacial polymerization, solvent evaporation, and cross-linking of polymers in solution.

10. The method of claim **1** wherein said pharmacologically active substance comprises a substance which has central nervous system activity but cannot cross the blood-brain barrier without modification or without a carrier.

11. The method of claim **1** wherein said pharmacologically active substance comprises a drug.

12. The method of claim **1** wherein said pharmacologically active substance comprises a diagnostic agent.

13. The method of claim **12** wherein said diagnostic agent is useful in the diagnosis for nuclear medicine and radiation therapy.

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